(such as bacille Calmette-Guérin and adenovirus), and novel recombinant DNA constructs may yet lead to promising efficacy results as a basis for large-scale testing. In the meantime, high-risk uninfected cohorts are now being recruited and the infrastructure put in place in the United States and abroad for efficacy tests of one or more of the most promising candidate HIV-1 vaccines that may become available in several years. The first vaccines used may be only partially effective, but their early introduction might still prevent many infections, reduce viral transmission, delay disease, and provide valuable information that could facilitate future vaccine development. Multiple vaccines that are tailor-made for the predominant HIV strain(s) circulating at different global sites may need to be tested simultaneously. A long-term commitment has been made to vaccine development; this must include realistic expectations and both preclinical and clinical trials.

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Laboratory Evaluation of Inherited Thrombotic Disorders

RECENT ADVANCES IN THE diagnosis of and therapy for thrombotic disease have focused attention on the consulting role of clinical pathologists in the laboratory evaluation of coagulation disorders. Patients referred for evaluation usually have venous thromboembolism, but some may have arterial thrombotic events. Inherited disorders that can be tested for in a coagulation laboratory may result from abnormalities in inhibitors of activated coagulation factors (antithrombin III, protein C, protein S), impaired clot lysis (dysfibrinogenemia, plasminogen deficiency, tissue-plasminogen activator deficiency, excess plasminogen activator inhibitor), or a metabolic disorder associated with vascular disease and thrombosis (homocystinuria).

Although only about 30% of patients with recurrent thrombosis have an inherited disorder identified, the yield of this evaluation can be improved by restricting it to young patients with recurrent thrombosis or patients with thrombosis and a positive family history. The laboratory evaluation should be deferred until two to three months after the acute event (to avoid acute-phase changes that may obscure a correct diagnosis) and after the patient has discontinued anticoagulant therapy. Many laboratories offer both functional and immunologic assays for evaluating these disorders. Because thrombotic disease may result from either quantitative deficiency or a qualitative abnormality of these proteins (for example, antithrombin III or protein C) and immunologic assays may yield normal results in patients with dysfunctional proteins, it is preferable to do functional assays that detect both types of disorders. Appropriate specimen collection, timing, and processing are critical, especially for fibrinolytic assays (tissue-plasminogen activator, plasminogen activator inhibitor). Deficiencies of proteins C and S and antithrombin III are thought to be the most common causes of inherited thrombosis. Previous studies indicating that fibrinolytic abnormalities were common causes of recurrent thrombosis have been recently challenged. A metabolic disorder, heterozygous homocystinuria, has been increasingly associated with arterial vascular disease and should be considered in middle-aged patients with premature arterial thrombosis.

One approach in the laboratory investigation of recurrent thrombosis is to first exclude acquired causes of hypercoagulability—hyperlipidemia, lupus anticoagulant, or malignancy. The presence of venous thrombosis should be initially evaluated with a functional protein C assay and a free protein S antigen assay. If the results of these tests are normal, a functional assay for antithrombin III can be done, followed by testing for dysfibrinogenemia. If the test results are normal, the fibrinolytic system could be evaluated.

Unexplained arterial thrombosis in young patients can be evaluated with an assay of plasminogen activator inhibitor activity, whereas middle-aged patients with premature arterial thrombotic events should be tested for heterozygous homocystinuria using a methionine loading test.

The importance of laboratory monitoring of anticoagulation has been emphasized by studies showing the clinical benefit of adequate heparin and warfarin therapy in treating thromboembolism. Because the responsiveness of commercial laboratory-activated partial thromboplastin time reagents may vary substantially, each laboratory should establish its therapeutic heparin range (activated partial thromboplastin time ratio, 1.5 to 2.5), so that it is equivalent to a heparin level of 200 to 400 U per liter (0.2 to 0.4 U per ml) by protamine titration. Despite the large body of published evidence indicating the clinical importance of using the international normalized ratio format in reporting laboratory prothrombin times, many coagulation laboratories do not use this format, leading to inappropriate anticoagulant therapy for many patients. Increased educational efforts will be necessary to inform practitioners and pathology personnel of the importance of rigorous laboratory control of anticoagulation.

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Enhancing Antibody and Its Role in Acquired Immunodeficiency Syndrome

ANTIBODIES AGAINST VIRAL proteins have traditionally been considered beneficial to the host by preventing infection. This principle has been the mainstay of modern vaccine development. It is now known, however, that certain antibody responses may not benefit the host but may, indeed, benefit the virus. One such phenomenon, antibody-dependent enhancement, increases the infectivity of a variety of viruses from several different families. Antibody-dependent enhancement can occur when nonneutralizing antibodies bind to viral surface proteins. The Fc portion of this antibody can then be bound by Fc receptors on macrophages. Viruses that are resistant to lysosomal degradation can then infect macrophages by this route. A second mechanism has been described whereby nonneutralizing antibodies bind to viral